Antimicrobial Susceptibility Testing Issues

Indiana State Department of Health

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Overview

- Physical Testing Issues:
  - Drugs Tested at Your Lab
- Interpretation Issues:
  - AST Breakpoint Revisions
  - Rewriting

The Label "CRE" is defined by:
1) The identity of the drugs tested against the isolate
2) The interpretation of these results

Physical Testing Issues: Drugs Tested in Your Lab

What drugs does a microbiology lab test for?

- Decision made by each lab.
- Lab should consult with infectious disease physicians, pharmacy, and infection control, and discuss:
  - Acceptable performance (*in vitro, in vivo*)
  - Industry standards
  - Costs
  - How to minimize emerging resistance
  - FDA clinical indications for use
  - Professional organization recommendations

CLSI Categories

- **Group A**: Routine, primary testing panels, always reported
- **Group B**: Primary testing, selective reporting
- **Group C**: Alternative or supplemental testing
- **Group U**: Urine only
- **Group O**: Generally not routinely tested in the USA
- **Group Inv.**: Investigational, not approved by the FDA

CLSI Categories, continued (*Enterobacteriaceae*)

Grouping	Drug
Group A	Ampicillin Cefazolin Gentamicin Tobramycin

CLSI Categories, continued

Grouping	Drug	
Group B	Amikacin Amoxicillin-clavulanate Ampicillin-sulbactam Ceftazidime-avibactam Ceftolozane-tazobactam Meropenem-vaborbactam Piperacillin-tazobactam	Cefuroxime Cefepime Cefotetan Cefoxitin Cefotaxime or ceftriaxone Ciprofloxacin Levofloxacin Doripenem Ertapenem Imipenem Meropenem Trimethoprim-sulfamethoxazole

CLSI Categories, continued

Grouping	Drug
Group C	Aztreonam Ceftazidime Ceftaroline Chloramphenicol Tetracycline
Group U	Cefazolin Fosfomycin Nitrofurantoin Sulfisoxazole Trimethoprim

Caveats …

- Certain drugs can't be reported from specific specimen types (ex. CSF, respiratory)
- Not every drug is tested, sometimes surrogates are used
- Some organisms have their own breakpoints (ex. *Salmonella, Shigella*)
- Sometimes a drug can only be tested by one particular test method (which isn't available in every lab)
- Sometimes a drug can only be tested for particular Genera or species:
  - Limited by FDA approvals
  - Limited by data availability (no breakpoints or ECV available for less-common species)

Data in Action, Indiana

How well does AST predict CP-CRE?

- Examined isolates June 1, 2016 – June 30, 2018
- n=1381
- Correlation between identifying a carbapenemase (gene) and the isolate being not susceptible (I or R) to carbapenems

	I/R to 1 drug	I/R to 2 drugs	I/R to 3-4 drugs
Carbapenemase found	52.2%	45.4%	79.7%

What are some other relevant technical issues for you to know related to AST and CRE?

- Colistin and Polymyxin B can only be tested/reported using broth microdilution (e.g. Sensititre®)
- New Combination Drugs: Ceftazidime-Avibactam, Meropenem-Vaborbactam, Ceftolozane-Tazobactam
  - Lag in when available on automated instrumentation
  - Etest/KB may be available
  - Must verify the new drugs (minimum 30 isolates per CLSI)
  - Difficulty in obtaining isolates (CDC/FDA AR Bank may help)

Interpretation Issues: AST Breakpoints

The Label "CRE" is defined by:

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Interpretive Category	Definition
Susceptible (S)	An isolate with an MIC at or below the established susceptible breakpoint. • Organisms are usually inhibited • Effective concentrations are achievable at the dosage and site of infection. • Likely to be clinically effective.
Intermediate (I)	An isolate with an MIC above the established susceptible breakpoint. • Effective concentrations are generally achievable in blood and tissues • Organisms may be inhibited, but at a lesser rate than for susceptible isolates • Likely to be clinically effective in body sites where drugs are physiologically concentrated or where a higher dosing of drug can be used. • May indicate a *buffer zone* between S and R.
Resistant (R)	An isolate with an MIC above the established susceptible breakpoint. • Effective concentrations are not generally achievable by normal dosing schedules • Clinical efficacy has not been reliably demonstrated

Your AST Report Says:		Your Interpretation:
Ceftazidime	>32	R
Ertapenem	1	I
Imipenem	1	S

Drug	Interpretative Category		
	S	I	R
Ceftazidime	≤4	16	≥32
Ertapenem	≤0.5	1	≥2
Imipenem	≤1	2	≥4

There are Different Breakpoints

- CLSI updates breakpoints as more information becomes available about drugs, bugs, and patient response to antibiotics
- CLSI publishes updates annually (Jan. of each year)
  - At least four significant breakpoint revisions have occurred for Gram Negative organisms since 2010
- Is your lab up-to-date on the current breakpoints?

Some relevant breakpoint revisions for you to know related to CRE:

- 3rd gen. Cephalosporins & Carbapenems (2010, 2012)

Drug	Type of Change	Previous			Current		
		S	I	R	S	I	R
Cefotaxime	decrease	≤8	16-32	≥64	≤1	2	≥4
Ceftazidime	decrease	≤8	16-32	≥64	≤4	8	≥16
Ceftriaxone	decrease	≤8	16-32	≥64	≤1	2	≥4
Ertapenem	decrease	≤2	4	≥8	≤0.5	1	≥2
Imipenem	decrease	≤4	8	≥16	≤1	2	≥4
Meropenem	decrease	≤4	8	≥16	≤1	2	≥4
Doripenem	decrease	**new**			≤1	2	≥4

How do I know which breakpoints I'm using?

Check the version of the CLSI document in your lab

- New breakpoints = CLSI M100-S29

How do I know which breakpoints I'm using?

- Check your instrument
- At what MIC does your instrument call ertapenem resistant? (one of the four major breakpoint changes)

Drug	Type of Change	pre-2010			Current		
		S	I	R	S	I	R
Ertapenem	decrease	≤2	4	≥8	≤0.5	1	≥2
Imipenem	decrease	≤4	8	≥16	≤1	2	≥4
Meropenem	decrease	≤4	8	≥16	≤1	2	≥4
Doripenem	decrease	**new**			≤1	2	≥4

What are some other relevant breakpoint revisions for you to know related to CRE?

- Cefepime (2014): Susceptible dose-dependent (SDD)
- Colistin (2017): Epidemiological cutoff values (ECVs)

Do labs really not update their breakpoints?

Ertapenem		
S	I	R
≤0.5	1	≥2

- Patient isolate has an ertapenem MIC of 2.0 µg/mL.
- By Current CLSI Breakpoints the isolate is **resistant**
- Hospital A is using old breakpoints. They report the isolate as **susceptible**.

Clinical Infectious Diseases

MAJOR ARTICLE

Carbapenem-Resistant *Enterobacteriaceae* Detection Practices in California: What Are We Missing?

Romney M. Humphries,[1] Janet A. Hindler,[1] Erin Epson,[2] Sam Horwich-Scholefield,[2] Loren G. Miller,[3,4] Job Mendez,[3] Jeremias B. Martinez,[3] Jacob Sinkowitz,[3] Darren Sinkowtiz,[4] Christina Hershey,[4] Patricia Marquez,[5] Sandeep Bhaurla,[5] Marcelo Moran,[5] Lindsey Pandes,[5] Dawn Terashita,[5] and James A. McKinnell[3,4,5]

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- Looked at hospital new-breakpoint implementation
- How long did it take to implement the new breakpoints?
- What was the impact on patient care? What was the impact on public health?

What did they find?

- New breakpoints were used in 72% of labs
- Implementation took 0-68 months (avg. 41 months)
- Not implementing new breakpoints caused labs to report false-susceptibility to carbapenems:

Drug	% Susceptible	
	Old	New
Ertapenem	8.9	< 1
Imipenem	18.6	< 1
Meropenem	18.6	< 1

Humphries, RM *et al.*, CID 2018

1 out of 5 isolates was falsely reported as susceptible to meropenem!

Humphries, RM *et al.*, CID 2018

Why were the breakpoints revised?

- Review of data:
  - PK-PD
  - Clinical data
  - MIC distributions (to include carbapenemase-producing strains, which were really new at the time)
- If a lab implemented the updated breakpoints, there was no longer a requirement that the lab do ESBL or carbapenemase testing for *clinical* purposes, it was still encouraged for *epidemiological* purposes
- If the lab has not implemented the revised breakpoints, the lab is *required* to perform ESBL and carbapenemase testing if the strain has an MIC of ≥2 μg/mL to any carbapenem

Interpretation Issues: Rewriting

The Label "CRE" is defined by:

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So do we still need to re-write drugs based on carbapenemase or ESBL results?

- It was also no longer recommended that results be re-written based on findings of an ESBL or carbapenem.
- This is a practice that still occurs today in some laboratory, and can significantly impact:
  - The number of antibiotics available to treat these infections!
  - Accuracy of public health data

Does this really happen?

Ertapenem		
S	I	R
≤0.5	1	≥2

- Patient isolate has an ertapenem MIC of ≤0.5 µg/mL.
- By Current CLSI Breakpoints the isolate is **susceptible.**
- Hospital A is using old breakpoints and guidelines. As the isolate is an ESBL-producer, they report the isolate as **resistant**.

What is the impact?

- Decreases the number of drugs available to:
  - Infectious Disease physician
  - Pharmacy
  - Infection Prevention
  - Public Health

- All pan-intermediate/intermediate isolates (by drugs tested at the clinical- and public health-lab) are investigated.

Drug	MIC	Interpretation
Ampicillin	<=2	*R
Ampicillin/Sulbactam	<=2	*R
Piperacillin/Tazobactam	<=4	*R
Cefazolin	>=64	R
Cefoxitin	>=64	R
Ceftazidime	2	*R
Ceftriaxone	>=64	R
Cefepime	2	*R
Meropenem	>=16	R

Isolate was determined not to be a carbapenemase producer by the PHL.

Conclusion

- **Knowledge is Power**: Know what methods your lab uses for AST, which drugs are tested, which drugs are reported, and why those decisions were made.
- **Make a Friend**: Realize that unless AST is one of your passions, that this field changes too rapidly to know every nuance; make a friend (lab manager or an ID doc?) that is familiar with these nuances.
- **Embrace Change**: AST recommendations change annually (usually based on increasing understanding of case management, new drugs, or changing epidemiology).

Questions?

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